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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,032	12/02/2003	Daniel S. Kohane	0492611-0532 (MIT 9851)	4419

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EXAMINER	
HOLT, ANDRIAE M	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
01/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/727,032	KOHANE ET AL.	
	Examiner	Art Unit	
	Andriae M. Holt	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42 and 44-55* is/are pending in the application.

4a) Of the above claim(s) *1-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-42 & 44-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 1, 2008 has been entered.

Claims 1-42 and 44-55 are pending. The restriction requirement and applicant's election, which are set forth in the Office Action of 10/12/2007, continue to apply in this RCE. Accordingly, Claims 1-34 stand withdrawn from further consideration as being directed to non-elected subject mater. Claims 35-42 and 44-55 will presently be examined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35-42, 44-51 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohane et al. (WO 98/51290).

Kohane et al. disclose combinations of naturally occurring site 1 sodium channel blockers such as tetrodotoxin (TTX) (tetrodotoxin, instant invention), saxitoxin, decarbamoyl saxitoxin and neosaxitoxin with other agents to give long duration block with improved features, including safety and specificity (page 3, lines 10-14). Kohane et al. disclose in one embodiment, duration of block is greatly prolonged by combining a toxin with a local anesthetic and glucocorticoid (page 3, lines 15-16)(site 1, sodium channel blocker, tetrodotoxin, local anesthetic and glucocorticoid, instant invention). Kohane et al. further disclose that bupivacaine is the preferred local anesthetic (page 11, lines 22-27) (bupivacaine, instant invention). Kohane et al. disclose corticosteroids that are useful to prolong in vivo nerve blockade include glucocorticoids such as dexamethasone (page 13, lines 2-3) (dexamethasone, instant invention). Kohane et al. further disclose in example 5, page 35, lines 1-21, the combination of tetrodotoxin with bupivacaine and epinephrine with 0.2% dexamethasone (tetrodotoxin, bupivacaine and dexamethasone in combination, instant invention). Kohane et al. disclose the combination of tetrodotoxin with bupivacaine provides blockade with durations of about 10 hours and the addition of dexamethasone can produce blockade in excess of 30 hours (page 35, lines 13-15). Kohane et al. teach in example 9, page 38, lines 1-13, the effect of the addition of dexamethasone to TTX and bupivacaine containing microspheres. Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic

acid) microspheres. Kohane et al. further teach the average duration of effective block was 7 days. Kohane et al. teach this represents a great improvement over bupivacaine-dexamethasone microspheres, which typically last 3 to 5 days.

Kohane et al. disclose that site 1 toxins do not produce the cardiac or convulsive systemic toxicities of existing local anesthetics. Kohane et al. further teach that combinations of site 1 toxins afford a way of providing prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis (page 7, lines 23-29).

Kohane et al. disclose local anesthetic is preferably delivered to the patient incorporated into a polymer in the form of microparticles, most preferably microspheres (page 14, lines 20-22). Kohane et al. further disclose other forms of the polymers include microcapsules, microencapsulated microspheres, slabs, beads, and pellets, which in some cases can also be formulated into a paste or suspension (pellets, instant invention) (page 14, lines 22-24). Kohane et al. disclose the anesthetic can be incorporated into the microsphere in a percent loading of 0.1% to 90% by weight, preferably 5% to 75% by weight (page 14, lines 8-10). Kohane et al. disclose the microspheres have a diameter of between approximately 10 and 200 microns, more preferably between 20 and 120 microns (col. 9, lines 60-62) (diameter less than 1 mm, 500 microns, 250 microns and 100 microns, instant invention).

Applicant defines an “effective amount” of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant further discloses that it will be appreciated by those of ordinary skill in this art; the effective

amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant discloses that it would be appreciated by one of skill in the art that the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teaches that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

Kohane et al. meet all of the limitations of the claims and thereby anticipate the claims.

The rejection of claims 35-42, 44-51, and 55 under 35 U.S.C. 102(e) as being anticipated by Kohane et al. (US 6,326,020) **is maintained**.

Claims 35-42, 44-51, and 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Kohane et al. (US 6,326,020).

Kohane et al. disclose combinations of naturally occurring site 1 sodium channel blockers (claims 35, 39 and 43, site 1 sodium channel blockers, instant invention), such as tetrodotoxin (TTX) (claim 39, tetrodotoxin, instant invention), saxitoxin, decarbamoyl saxitoxin and neosaxitoxin with other agents to give long duration block with improved features, including safety and specificity (col. 2, lines 30-35). Kohane et al. disclose in one embodiment, duration of block is greatly prolonged by combining a toxin with a local anesthetic and glucocorticoid (col. 2, lines 36-38)(claims 35, 39-41 and 43, site 1, sodium channel blocker, tetrodotoxin, local anesthetic and glucocorticoid, instant invention). Kohane et al. further disclose that bupivacaine is the preferred local anesthetic (col. 7, lines 21-22) (claim 40, bupivacaine, instant invention). Kohane et al. disclose corticosteroids that are useful to prolong in vivo nerve blockade include glucocorticoids such as dexamethasone (col. 7, lines 1-2) (claims 40 and 42, dexamethasone, instant invention). Kohane et al. further disclose in example 5, col. 20, lines 26-52, the combination of tetrodotoxin with bupivacaine and epinephrine with 0.2% dexamethasone (claims 35 and 39-43, tetrodotoxin, bupivacaine and dexamethasone in combination, instant invention). Kohane et al. disclose the combination of tetrodotoxin with bupivacaine provides blockade with durations of about 10 hours and the addition of dexamethasone can produce blockade in excess of 30 hours (col. 20, lines 38-52). A

combination of tetrodotoxin, bupivacaine and dexamethasone is taught at col. 4, lines 20-25.

Kohane et al. disclose local anesthetic is preferably delivered to the patient incorporated into a polymer in the form of microparticles, most preferably microspheres (col. 2, lines 65-67). Kohane et al. further disclose other forms of the polymers include microcapsules, microencapsulated microspheres, slabs, beads, and pellets, which in some cases can also be formulated into a paste or suspension (pellets, instant invention). Kohane et al. disclose the microspheres have a diameter of between approximately 10 and 200 microns, more preferably between 20 and 120 microns (col. 9, lines 60-62) (diameter less than 1 mm, 500 microns, 250 microns and 100 microns, instant invention). Kohane et al. disclose in example 9, the effect of the addition of dexamethasone to TTX and Bupivacaine containing microspheres (col. 22, lines 10-25).

Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant' further discloses that it will be appreciated by those of ordinary skill in this art, the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant further discloses that it would be appreciated by one of skill in the art , the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teaches that anesthetic, an

active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

Kohane et al. meet all of the limitations of the claims and thereby anticipate the claims.

Response to Arguments

Applicant's arguments filed December 1, 2008 have been fully considered but they are not persuasive. Applicant argues that Kohane fails to teach any of the components that comprise the composition in an amount sufficient to treat any of the listed conditions.

In response to applicant's argument, Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired

biological response. Applicant' further discloses that it will be appreciated by those of ordinary skill in this art; the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant further discloses that it would be appreciated by one of skill in the art; the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teach that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

The claims remain rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 35-36 and 39-42 under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Levin (US 2002/00101094) **is maintained**.

Claims 35-36 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Levin (US 2002/00101094).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist. Applicant claims amount of the combination of the components in the composition is effective to treat epilepsy, cardiac arrhythmias or preterm labor. The electrically excitable tissue includes brain, heart and uterine tissue.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kohane et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above. Kohane et al. also teach that bupivacaine is a particularly long acting and potent local anesthetic when incorporated into a polymer. Kohane et al. teach that its other advantages include sufficient sensory anesthesia without significant motor blockage, lower toxicity and wide availability (col. 7, lines 24-28).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not explicitly teach that the electrically excitable tissue is brain tissue. It is for this reason Levin is added as a secondary reference.

Levin teaches pharmaceutical compositions useful for inhibiting a cerebral neurovascular disorder or a muscular headache in a patient (page 6, paragraph 64). Levin teaches that cerebral neurovascular disorders may be selected from the group

consisting of cerebravascular spasm, seizure, and a neurovascular headache (page 5, paragraph 59)(claim 36, brain tissue, instant invention). Levin teaches the long acting anesthetic pharmaceutical composition comprises a pharmaceutically acceptable carrier and at least one local anesthetic ingredient selected from the group consisting of a long-acting local anesthetic, a persistent local anesthetic and a sustained release formulation of a local anesthetic (page 6, paragraph 60). Levin further teaches in claim 5, page 32, the local anesthetic is bupivacaine (claims 35, 40 and 43, local anesthetic, bupivacaine, instant invention). Levin teaches in an alternate embodiment the long acting local anesthetic pharmaceutical composition further comprises a pharmaceutically active agent such as tetrodotoxin and a glucocorticoid compound (page 6, paragraph 61) (claims 35, 39-43, tetrodotoxin, local anesthetic and glucocorticoid receptor agonist).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. and Levin to produce a pharmaceutical composition that would be effective in treating a disorder that affects brain tissue. As taught by Kohane et al. the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. It is known in the art that nerve tissue is electrically excitable tissue. Levin teaches that a local anesthetic composition alone or in combination with tetrodotoxin or a glucocorticoid

compound is effective in treating cerebral neurovascular disorders. Thus, as the compositions safely and effectively treat disorders of electrically excitable tissues, one skilled in the art at the time of invention would have been motivated to combine the teachings.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Response to Arguments

Applicant's arguments filed December 1, 2008 have been fully considered but they are not persuasive. Applicant argues that no combination of the references teaches or suggests the presently claimed invention, specifically; none of the references teach components of the components in effective amounts to treat epilepsy, cardiac arrhythmias or pre-term labor.

In response to applicant's argument, Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant' further discloses that it will be appreciated by those of ordinary skill in this art; the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant further discloses that it would be

appreciated by one of skill in the art; the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teach that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

The skilled artisan would have been motivated to combine the teachings of Kohane et al. and Levin and use the composition to suppress electrical activity in brain tissue, in particularly by treating epilepsy because Levin teaches that a local anesthetic composition alone or in combination with tetrodotoxin or a glucocorticoid compound is effective in treating cerebral neurovascular disorders. Epilepsy is a cerebral neurovascular disorder. In addition, Kohane et al. teach that site 1 toxins do not produce the cardiac or convulsive systemic toxicities of existing local anesthetics. Given the

state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to use the combination to treat epilepsy because combinations of site 1 toxins and other active agents afford a way of providing prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis.

The claims remain rejected.

The rejection of claims 35-42 under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Webb et al. (US 2001/002404) **is maintained.**

Claims 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Webb et al. (US 2001/002404).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist. Applicant claims amount of the combination of the components in the composition is effective to treat epilepsy, cardiac arrhythmias or preterm labor. The electrically excitable tissue includes brain, heart and uterine tissue.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kohane et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not teach the electrically excitable tissue being heart and uterine tissue. It is for this reason Webb is added as a secondary reference.

Webb et al. teach that conjugates of pharmaceutical agents and a highly lipophilic group, a C8-C26, naturally occurring unbranched carbon chain, have a different selectivity relative to the unconjugated pharmaceutical agents (page 2, paragraph 19). Webb et al. teach in one embodiment, the conjugates render the activity of these conjugates selective for colon tissue, breast tissue and central nervous system tissue (page 2, paragraph 20) (claim 36, brain tissue (nervous system), instant invention). Webb et al. teach that a method is provided for targeting a therapeutic agent to noncentral nervous system tissue to treat a noncentral nervous system condition (page 2, paragraph 21). Webb et al. further teach the noncentral nervous system tissue can be tissue from the cardiovascular system including heart and vascular system (claim 37, heart tissue, instant invention) and reproductive system including uterus (claim 38, uterine tissue, instant invention) (page 2, paragraph 21-page 3 paragraph 21). Webb et al. teach that the pharmaceutical agent may be any pharmacological compound or diagnostic agent (page 3, paragraph 24). Webb et al. further teach that anesthetic agents include bupivacaine (page 12, paragraph 105)(claim 40, local anesthetic, bupivacaine, instant invention). Webb et al. also teach that glucocorticoid

agents include dexamethasone (page 21, paragraph 212) (claims 41-42, glucocorticoid receptor, dexamethasone).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. and Webb et al. and produce a pharmaceutical composition that would be effective in treating a disorder that affects brain, heart and uterine tissue. As taught by Kohane et al., the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. One skilled in the art at the time the invention was made would have been motivated to use the composition to treat disorders that affect brain, heart and uterine tissue because Webb et al. teach that the combination of a pharmaceutical agent with a fatty acid provides a method for selectively targeting pharmaceutical agents to desired tissues. Webb further teaches agents claimed in the instant invention as agents that are used in the compositions.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Response to Arguments

Applicant's arguments filed December 1, 2008 have been fully considered but they are not persuasive. Applicant argues that no combination of the references teaches or suggests the presently claimed invention, specifically; none of the references teach components of the components in effective amounts to treat epilepsy, cardiac arrhythmias or pre-term labor.

In response to applicant's argument, Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant' further discloses that it will be appreciated by those of ordinary skill in this art; the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant further discloses that it would be appreciated by one of skill in the art; the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teach that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the elected invention and the amount of each active agent used in the

composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac

The skilled artisan would have been motivated to combine the teachings of Kohane et al. and Webb et al. and use the composition to suppress electrical activity in brain tissue, heart tissue, and uterine tissue, in particularly by treating epilepsy, cardiac arrhythmias and pre-term labor because Webb et al. teach that the combination of a pharmaceutical agent with a fatty acid provides a method for selectively targeting pharmaceutical agents to desired tissues. In addition, Kohane et al. teach that site 1 toxins do not produce the cardiac or convulsive systemic toxicities of existing local anesthetics. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to use the combination to treat epilepsy because combinations of site 1 toxins and other active agents, in particular anesthetics and glucocorticoid receptor agonists, afford a way of providing prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis.

The claims remain rejected.

The rejection of claims 52-54 under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of ten Cate (US 6,352,683) **is maintained**.

Claims 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of ten Cate (US 6,352,683).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist that is provided in a microparticle. Applicant further claims the composition comprises a targeting agent and that the microparticles are triggered to release the agent.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kohane et al. have been discussed earlier in this Office action and the discussion there are incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not expressly teach the addition of a targeting agent of claim 52 or that the microparticle is triggered to release by radio-frequency, beams or any of the

other methods stated in claim 54. It is for this reason ten Cate is added as a secondary reference.

ten Cate teaches a local and site-specific drug delivery system for delivering a drug to a specific site (col. 2, lines 42-43). ten Cate teaches the drug delivery system is characterized by the combination of a) a carrier material which reflects, absorbs, or emits electromagnetic or mechanical vibrations enabling the monitoring of the material, b) a drug associated with the carrier material and c) local-delivery means for delivering the carrier material and the drug to the specific site (col. 2, lines 44-50) ten Cate teaches the drug delivery system may also include means for inducing release of the drug from the carrier material when the carrier material is at the specific site, such as means for generating electromagnetic or mechanical vibrations(col. 2, lines 55-59) (triggers, magnetism, instant invention).

ten Cate teaches the carrier material may comprise an ultrasonic contrast agent in the form of microparticles, microbubbles, microspheres, or microcapsules (col. 2, lines 60-62). ten Cate teaches the local-delivery means may comprise a targeting agent associated with the carrier material. ten Cate further teaches the targeting agent is capable of binding to the specific site within the individual (col. 2, lines 65-67-col. 3, line 1). ten Cate teaches the targeting agent may be a protein or an antibody (col. 3, lines 1-5) (antibodies, proteins, instant invention). ten Cate teaches the drug used in the composition may include dexamethasone (col. 3, lines 11-20).

ten Cate teaches the local and site specific drug delivery system is intended to be a system which is capable of transferring or carrying a drug to a specific area or site,

at which the system releases the drug in an active or controlled manner enabling the interaction of the drug with the specific area or site, prior to or after administration of the drug delivery system to the human (col. 4, lines 60-67).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. and ten Cate and use a targeting agent in the composition. As taught by Kohane et al., the combination of tetrodotoxin, bupivacaine and dexamethasone in microspheres produces a longer block than the combination without microspheres (5 to 20 days), which is useful for chronic pain and cancer pain.

One skilled in the art at the time the invention was made would have been motivated to add the targeting agent to provide drug delivery to specific areas or sites that need treatment, as ten Cate teaches targeting agents do. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to provide a micoparticle composition that targets the specific area or site that needs treatment and that provides prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Response to Arguments

Applicant's arguments filed December 1, 2008 have been fully considered but they are not persuasive. Applicant argues that no combination of the references teaches or suggests the presently claimed invention, specifically; none of the references teach components of the components in effective amounts to treat epilepsy, cardiac arrhythmias or pre-term labor.

In response to applicant's argument, Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant' further discloses that it will be appreciated by those of ordinary skill in this art; the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant further discloses that it would be appreciated by one of skill in the art; the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teach that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this

composition is the elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

Therefore, the skilled artisan would have been motivated to combine the teachings of Kohane et al. and ten Cate and use a targeting agent in the composition to deliver the composition to the targeted tissues. Particularly to brain tissue, heart tissue and uterine tissue to treat epilepsy, cardiac arrhythmias, and pre-term labor because ten Cate teaches the local and site specific drug delivery system is intended to be a system which is capable of transferring or carrying a drug to a specific area or site, at which the system releases the drug in an active or controlled manner enabling the interaction of the drug with the specific area or site, prior to or after administration of the drug delivery system to the human.

The claims remain rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is (571)272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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